REMARKS

With this response, claims 44, 46, 50, 52, 54-58, 60, 61, 63, 64, 66, 67, 69, 70, 72, 73, 75, 76, 78, 79, and 81-82 have been canceled, without prejudice or disclaimer. Thus, upon entry of the present response, claims 83-86 and 90-94 will be pending.

Canceled claims 60-61, 63-64, 66, 72-73, 75, 78-79, and 81-82, which are indicated in the current Office Action as allowable, are currently being pursued in copending continuation application no. 11/127,046 filed May 10, 2005.

Applicant acknowledges, with appreciation, that the Examiner has deemed chimeric and humanized antibodies to be enabled at the time of the invention in 1992. Office Action at 2-3. *See also* Capon v. Eshhar, No. 03-1480, 2005 U.S. App. LEXIS 16865, at 12-13 (Fed. Cir. Aug. 12, 2005) (claims to chimeric genes comprising antibody fragment constructs were presumed to be enabled as of 1992).

Written Description

The Examiner has rejected claims 83-86 and 90-94 under 35 U.S.C. § 112, first paragraph, as lacking written description in the disclosure of the application sufficient to reasonably convey to one of skill in the art that the inventor had possession of the invention at the time the application was filed. Office Action at 4-7. Applicant submits that these claims have adequate written description in the specification as filed.

The Examiner cites the requirements for adequate written description of claims relating to human and genus forms of CD40CR antigen as set forth by the Federal Circuit in Noelle v. Lederman, 355 F.3d 1343, 69 USPQ2d 1508 (Fed. Cir. 2004; Noelle). The Examiner states that "relevant identifying characteristics" such as structure or other physical and/or chemical characteristics of the CD40CR antigen are not set forth in the specification as filed, commensurate in scope with the invention as claimed. The Examiner specifies that description of the structural features of the CD40CR antigen and a correlation between the chemical structure and function of

the genus of CD40CR antigens is required, and that disclosure of the mouse CD40CR antigen is insufficient to support claims directed toward all mammalian and human CD40CR antigens.

In response, Applicant submits that there is complete written description and thus full characterization of the antigen recognized by antibodies of the invention.

The present claims recite use of an antibody that recognizes a well-characterized antigen, based on structural and functional characteristics expressly set forth in writing (the written description) in the specification. One characteristic of the antigen, a defining characteristic, is its specific interaction with CD40-Ig. In other words, the antigen (like many) is characterized in part by a specific binding partner. CD40-immunoglobulin (CD40-Ig) is a fusion protein comprising the extracellular binding domain of the human CD40 protein joined to a portion of an antibody immunoglobulin chain (*see* the specification at page 22, line 23 to page 23, line 3, and Figure 8). CD40 is the B-cell ligand of the CD40 T-cell counter-receptor (CD40CR), variously referred to as CD40 ligand, CD40L, or gp39, as well as CD40CR in this application. CD40 binds to CD40CR on activated T-cells, which initiates B-cell activation. The amino acid sequence of the human CD40 binding domain of CD40-Ig is described and enabled in the specification. With a disclosed sequence and structure, the CD40-Ig construct is easily envisioned by one of skill in the art. The skilled artisan, given the CD40-Ig construct, would appreciate that the inventor has possession of any antigen that binds the CD40-Ig construct.

The present application further provides specific examples of T-cell antigens bound by CD40-Ig. One such antigen, characterized in extensive biochemical detail, is the murine CD40CR molecule (*see* the specification at page 28, line 8, to page 30, line 35). Another, characterized implicitly because the CD40 part of the CD40-Ig molecule is a human CD40, is human CD40CR. The specification further provides an example of CD40-Ig binding to human T cells (*see* the specification at page 31, lines 20-31, and Figure 7).[1]

[1] The argument raised by party Lederman during the Noelle v. Lederman interference, that this example is suspect because of the absence of appropriate scientific controls, represents a case of the improbable overruling the probable. It elevates the remote, unlikely possibility that *human* CD40 molecule is not driving binding to an *activated* human T cell. Moreover, it is irrelevant. The inventor interpreted this binding to represent binding to CD40CR on human T cells, and

It would be routine for one of skill in the art to make CD40-Ig following the explicit recipe in the application, and use this as a "touchstone" to identify CD40CR protein. CD40-Ig is a template that gives the structure of the antigen. The antigen is further defined by molecular weight (a physical characteristic) and expression on activated but not resting T-cells (a functional characteristic) (*see* the specification at, *e.g.*, page 15, lines 15-21, and page 28, line 8, to page 30, line 35, and Figures 3, 4, and 6). The application teaches antibodies binding to the antigen as well as uses for such antibodies (*see* the specification at pages 11-13 and 17-19). As such, the antigen of the invention as claimed, antibodies to this antigen, and the uses of antibodies that bind to this antigen are adequately described in the specification as filed.

Applicant notes that the Examiner's reasoning for rejecting the pending claims does not pertain to features the claims recite. In particular, the Examiner states, citing Noelle, that the specification does not support "the entire genus of CD40CR antigens as it reads on mammalian and human[2] CD40CR antigens." Office Action at page 5, paragraph 4. Applicant respectfully notes that no rejected claim recites such language. In particular, no claim recites CD40CR. Instead, the claims recite specific structural and functional features of the antigen that satisfy the requirement for a well-characterized antigen. As described above, these structural features include: (1) sequence and conformation to permit binding with a soluble human CD40-Ig construct defined by SEQ ID NOs: 2 and 3;[3] and (2) a molecular weight of the molecule precipitated by this soluble CD40-Ig construct. Moreover, although sufficient to fully characterize the CD40CR antigen recognized by the antibody recited in the claims, the specification discloses functional characteristics of this antigen that are also recited in the claims: (1) its presence on activated, but not resting, T cells; and (2) its pre-clearance by precipitation with the soluble human CD40-Ig construct. Finally, the antibody recited in the claims, which as an antibody has a structure that the PTO has stated needs no further elaboration, is also characterized by novel functions: it binds to the antigen, it blocks binding

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described it as such. Thus, the written description is in the specification. The skilled artisan would understand what this meant. Nothing in the extensive record suggests any such failure of understanding. The interpretation of the data, however preliminary, as substantiating any other interaction creates an issue where none exists. One does well to remember Occam's razor: the simplest explanation is most likely the correct one.

[2] Applicant respectfully notes that "human CD40CR" is a species of CD40CR.

[3] Binding of CD40-Ig is implicit to both the precipitation and pre-clearance limitations of the claims.

of the CD40-Ig construct to activated T cells, and it inhibits T cell induction of B cell activation. Unfortunately, the Examiner's rejection does not consider these limitations, which find literal support in the specification. There is no doubt that the written description of the specification supports the invention as *presently claimed.* With the facts of the claims and corresponding written description in mind, Applicant now considers the legal context of the proper analysis of the requirement.

The written description requirement of 35 U.S.C. 112, ¶ 1, has been interpreted as a provision whereby the applicant shows possession of the claimed invention by fully describing the invention such that the applicant can "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." Vas-Cath, Inc., v. Mahurkar, 935 F.2d 1555, 1563 (italics omitted). The U.S. Patent and Trademark Office states that "the 'essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." Guidelines for the Examination of Patent Applications under the 35 U.S.C. 112, para. 1, "Written Description" Requirement, Federal Register, Vol. 66, No. 4, 1099, 1104 (2001).

The court in Capon v. Eshhar, No. 03-1480, 2005 U.S. App. LEXIS 16865 (Fed. Cir. Aug. 12, 2005; Capon) clarified Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997; Lilly) by stating that there is no "per se" rule under 35 U.S.C. § 112 of what information must be recited in the specification (Capon at 23). The Federal Circuit in Capon held that the written description requirement "must be applied in the context of the particular invention and the state of the knowledge" (Capon at 23). Under Capon, the determination of adequate support for generic claims to biological subject matter "depends on a variety of factors, such as the existing knowledge in the field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter" (Id. at 26). Further, the scope of each claim must be separately considered (Id. at 21).

In Lilly, the court held a patent invalid for lack of written description because the patent claimed the entire genus of vertebrate cDNAs encoding insulin, while the patent specification disclosed only the sequence for rat insulin cDNA. The court held that a DNA cannot be adequately described solely by a description of its function or the desired result of its use. Instead, adequate written description of *any* specific DNA (such as "human insulin DNA") requires disclosure of the nucleotide sequence encoding the gene. Further, claims to a genus of DNAs (such as "vertebrate insulin DNA") are adequately described either by recitation of the DNA sequences of a representative number of species, or by the disclosure of shared structural features of the genus.

The decision in Lilly held as invalid claims covering the genus of vertebrate insulin DNA, and particularly human insulin DNA, where only the rat DNA sequence was provided in the specification. These claims were held invalid despite disclosure of the rat sequence and a protocol by which human (or other mammalian) DNA could be isolated from the rat sequence. The court stated that the redundancy of the genetic code "permits one to hypothesize an enormous number of DNA sequences" that may code for any given protein. Lilly, 119 F.3d 1559 at 1567, quoting In re Deuel, 51 F.3d 1552, 1558 (1995). Therefore, a gene is not described by reference to the protein it encodes. Under Lilly, disclosure of a genetic invention requires a nucleotide-by-nucleotide recitation of the invention. *See* Moba, B.V., Staalkat, B.V., and FPS Food Processing Systems, Inc., V. Diamond Automation, Inc., 325 F.3d 1306, 1324 (Fed Cir. 2003; Moba).

The Lilly standard was specific for DNA: "An adequate written description *of a DNA*... requires a precise definition, such as by structure, formula, chemical name, or physical properties." Lilly at 1566 (italics added). The court further held that "a description of rat insulin *cDNA* is not a description of the broad classes of vertebrate or mammalian insulin *cDNA*." Lilly at 1568 (italics added). Indeed, the court in Lilly "specifically highlighted the distinct nature of DNA as it considered whether particular types of description adequately demonstrate that the inventor possessed the claimed DNA." Carnegie Mellon University and Three Rivers Biologicals, Inc., v. Hoffman-La Roche Inc., et al., 148 F.Supp.2d 1004, 1014-1015 (Fed. Circ. 2001; Carnegie Mellon).

Thus, the Lilly written description analysis, like all properly considered written description analysis, is limited to the facts of the case. In Lilly, the applicants claimed DNA encoding human insulin, and DNA encoding mammalian insulin, without providing a description of the structure defining either. Thus, the specification did not *describe* in words the subject matter expressly claimed. Had the patentee claimed the subject matter using words commensurate with the invention, such as a DNA encoding an insulin protein (a functional limitation with implicit sequence/structure), hybridizable to the DNA encoding rat insulin or having some defined percent identity to DNA encoding rat insulin, the analysis and outcome would have been necessarily different. Lilly does not establish a *per se* rule. It establishes a fact-driven analysis that requires the claims to recite limitations supported by the specification.

The Lilly standard was incorporated into the U.S. Patent and Trademark Office (PTO) Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement (Federal Register, Vol. 66, No. 4, pages 1099-1111, 2001) and the accompanying Synopsis of Application of Written Description Guidelines (available at www.uspto.gov/web/patents/guides.htm). The Guidelines and Synopsis are not binding law, but both the Guidelines and the Synopsis are cited and respectfully followed in current caselaw. *See*, e.g., Enzo Biochem v. Gen-Probe, Inc., 323 F.3d 956, 964 and 967-8 (Fed. Cir. 2002; Enzo II), Chiron Corporation v. Genentech, Inc., 268 F.Supp.2d 1148, 1162-63; Carnegie Mellon at 1017; Noelle at 1349.

The Synopsis outlines examples for Patent Office Examiners to assess the adequacy of written description to support the claimed invention in patent applications, based on actual patent applications. There are 13 examples relating to the field of biotechnology; the majority relate to DNA and genetic species, while one example relates to antibody technology.

Example 9 of the Synopsis describes a hypothetical application where the specification discloses the sequence of a cDNA (Synopsis, Example 9, p. 35-37). The complement of this cDNA sequence is used to isolate similar nucleic acids under highly stringent hybridization conditions.

The nucleic acids characterized by the ability to hybridize to the specified sequence are expressed as protein products (a function based on structure). They are not characterized by sequence. Given this disclosure, claims to the genus of nucleic acids that hybridize to the sequenced cDNA and encode proteins with a function similar to the function of the protein encoded by the cDNA have adequate written description support. The Example states that the sequenced cDNA falls within the scope of the claimed genus and has been reduced to practice. Example 9 further states that hybridization techniques using a known DNA, much like techniques to make antibodies that bind to an antigen as discussed in Example 16 below, are conventional in the art. Therefore, the claims are adequately described and lack of compliance with the written description requirement raises no bar to patentability.

Synopsis Example 16 defines an antigen, "antigen X", as "well characterized" when it is defined in the specification as follows: 1) antigen X is purified by gel filtration and defined by molecular weight; 2) a clear protocol for the isolation of antigen X is provided in the specification; along with 3) contemplation in the specification of antibodies which bind to antigen X and uses of such antibodies (Synopsis, Example 16, p. 59-60). Based on these parameters, the applicants of the application have provided a "well characterized" antigen.

Example 16 states that antibodies are structurally well characterized, and that the level of skill and knowledge in the art is such that production of antibodies against a well-characterized antigen is conventional. Based on such a well-characterized antigen, claims relating to an antibody "capable of binding to antigen X" are adequately described and have no written description bar to patentability.

The decision in Enzo Biochem v. Gen-Probe, Inc., 323 F.3d 956, 980-81 (Fed. Cir. 2002; Enzo II) emphasizes that "the functional characteristic of preferential binding... coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed" fulfills the written description requirement. However, the structural characteristics of the claimed DNA sequences in Enzo II were not disclosed in the specification; rather, the specification referred

to deposited sequences and provided disclosure on how to obtain and utilize the sequences. Therefore, under Enzo II, written description is fulfilled by providing a functional binding moiety plus providing the means to further define the invention using reagents disclosed in specification combined with teachings on how to use the reagents. Put another way, possession can be shown by a functional binding description plus an enabling disclosure. This is adequate for written description and raises no enablement issue.

Chiron Corporation v. Genentech, Inc., 268 F. Supp. 2d 1148 (Fed. Cir. 2002; Chiron) supports the art-understood concept that antibodies can be claimed by describing the antigen to which the antibodies bind. Chiron additionally supports the principle that an antigen can be defined by the antibodies that bind it. The court in Chiron stated that physical properties of the HER2 antigen were disclosed by breast cancer cell lines and tissue sections in which it is found (by antibody binding), as well as by the disclosure of the antibodies that bind to the antigen and an approximate molecular weight of the antigen (isolated by applying a binding antibody to a protein gel). The court in Chiron cites a declaration by an expert that *as of 1985* it was common to identify an antigen by a molecule that specifically bound to it, such as an antibody (Chiron at 1163). This is fully seven years prior to the time of the present invention. The court found that disclosure of antibodies that bind to an antigen, and a disclosure of where the antigen is present in cells in addition to the approximate molecular weight of the antigen, supports the conclusion that one of skill in the art as of 1985 would have found the antigen and antibodies to have been adequately described in the application (Id.). Thus, once an antibody to an antigen is identified, additional physical characteristics of the antigen—where it is present in cells or tissues, and its molecular weight as determined by Western Blot—can be supplied by using that antibody and support in the specification to provide adequate written description of the antigen.

Review of the case law and the PTO Guidelines and Synopsis establish that (1) antibodies to a well characterized antigen meet the written description requirement; and (2) an antigen is well characterized by reference to a fully enabled specific binding partner. The written description of the application provides both. It provides, and the claims recite, the sequence of the

part of theCD40 molecule that specifically recognizes the antigen, as well as a complete description of a functional CD40-Ig construct. *See* Chiron; Enzo II.[4] Because the specification sets forth the complete sequence, there is no need for a deposit. In addition, the specification sets forth functional characteristics of the antigen, and the antibody that binds to it, that further evidence possession of the invention. *See* Lilly; Enzo II.

Claims 83-86 and 90-94 of the instant application call for an antibody binding to an antigen that: (a) is present on activated but not resting T-cells; (b) has the same molecular weight as a protein precipitated by a CD40-immunoglobulin (CD40-Ig) fusion protein comprising the extracellular domain of a CD40 protein having the amino acid sequence of SEQ ID NO:2 and an extracellular domain at the site of fusion having the amino acid sequence of SEQ ID NO:3; and (c) is pre-cleared by precipitation with the CD40-Ig; which antibody blocks binding of the CD40-Ig to activated T-cells and T-cell induction of B-cell activation. Accordingly, in the present claims, the antigen is characterized by structural characteristics, cell distribution characteristics, and ligand-binding characteristics, and the antibody is characterized by antigen-binding and functional characteristics, as discussed in detail below.

Antigen Physical Characteristics: The antigen has the same molecular weight as a protein bound by Applicant's CD40-Ig construct, which has a ligand-binding domain fully characterized by amino acid sequence (SEQ ID NO:2). The antigen was and can be isolated and tested for molecular weight using methods identical to those employed in Example 1, page 28, lines 8-30 (Figure 4) and page 29, lines 13-17 (Figure 5b). Starting materials for the antigen can be cell membranes from activated helper T cells, prepared as described on page 21, lines 20-35; or as

[4] It is noted that both in the present application (*see, e.g.*, allowable claim 60) and in patent references cited by the Examiner (*see* Lederman et al., U.S. Patent No. 5,993,816), claiming antibodies by virtue of their binding to a defined ligand is deemed by the Patent Office to comply with the written description requirement. This demonstrates again that a molecule can be described by reference to a specific binding partner. Thus, an antigen may be characterized by binding to an antibody or to a defined protein. As noted above, the CD40-Ig construct has a defined amino acid sequence as recited in claims 83-86 and 90-94.

described in Example 2 (page 31, lines 20-31). As described on page 29, lines 16-17 and in Figure 5b, using plasma membranes from murine helper T-cells, CD40-Ig recognized a 39 kD protein.[5]

Antigen Cell Distribution Characteristics: As described in Example 1, page 28, lines 8-30, the antigen is expressed on activated but not resting helper T-cells. This was shown in a binding assay where activated helper T-cells stained 56% positive with CD40-Ig but not with the control construct CD7E-Ig (*Id.*).[6]

Antigen Ligand-Binding Characteristics: The antigen is pre-cleared by precipitation with CD40-Ig. *See* page 29, lines 18-22. This shows that the antigen is a member of a specific binding pair with CD40-Ig. *See* Chiron; Enzo II.

Antibody Antigen-Binding Characteristics: The antibody blocks the specific binding of CD40-Ig to activated helper T-cells. This shows that the antibody and CD40 have overlapping or identical binding epitopes on the antigen (page 29, lines 8-13). This is a unique characteristic of the antibody in the claimed methods.

Functional Characteristics: The antibody has the functional characteristic of inhibiting T-cell activation of B-cells. This is supported by, *e.g.*, Example 1, page 28, line 35 to page 29, line 30, of the original specification, where it is shown that MR1 antibody blocked B-cell activation while control antibodies did not.

The Examiner cites Skolnick et al. (Trends in Biotech. 18:34-39, 2000) in support of the argument that assigning functional activities to a protein or protein family based on sequence homology is inaccurate and requires experimental research to confirm the function of a particular protein. Applicant respectfully responds that no functional activities were assigned based on sequence homology in this application; rather, the application reveals that antigens with distinct cellular distribution and shared structural features—namely, antigens located on activated T-cells

[5] Antibody MR-1 also recognized this 39 kD protein.
[6] In addition, as described on page 29, lines 2-4, MR1 recognized an antigen that was selectively expressed on activated murine helper T- cells.

and with a structure that binds to the CD40-Ig template—are capable of mediating T-cell induction of B cell activation.

The Examiner cites the court decision in Noelle that Noelle's application lacked written description for the genus of CD40CR antigens, and that the skilled artisan lacked a reasonable likelihood of success in isolating human CD40CR antigen given mouse CD40CR antigen. In response, Applicant respectfully points out that the "reasonable likelihood of success" issue was raised by the Board of Patent Appeals and Interferences ("Board") while determining whether an interference-in-fact existed between the claims of the Noelle application and those of the Lederman patent (*see* Noelle at 1347-48). This finding was *not* related to the Board's determination of written description of the invention, and is not applicable here.

Ultimately, the Examiner agrees with the Applicant's position:

> ... the [Written Description] requirement may be alternately met by ... disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus" (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday, January 5, 2001; see especially page 1106, column 3).

Office Action, page 6, paragraph 4. As pointed out in detail above, the present claims recite this combination of structural and functional features that show that the applicant was in possession of the *claimed* genus.

With respect to the outcome of the interference captioned Noelle v. Lederman, Applicant reiterates: *these are different claims*. Not only are they method claims, which were not included in the interference, these claims recite different limitations with respect to the antigen, limitations that the written description expressly supports. The Examiner is charged with examining the pending claims, not claims that are not pending.

For all of the above reasons, it is clear that the specification adequately supports claims 83-86 and 90-94. Antibodies binding the antigen bound by the CD40-Ig construct have more than adequate written description support in the disclosure of the application as filed. Reconsideration and withdrawal of this rejection is therefore earnestly requested.

Enablement

The Examiner rejects claims 57-58, 67, 69-70, 83-86, and 90-94 as lacking enabling disclosure in the specification as filed. The rejection of claims 83-86 and 90-94 for non-enablement of any "antigen having the characteristics recited in instant claims [at] (a)-(c)" is addressed in detail below. The rejection of the remaining claims, Office Action at 10-11, is rendered moot by their cancellation herein.

The Examiner requests identification of the genus of CD40CR antigens by molecular weight, amino acid composition, sequence, etc. The Examiner states that, while the specification is enabling for the protein recognized by the MR1 antibody, the specification does not enable any antigen having the characteristics recited in claims 83-86. The Examiner alleges that the application discloses no more than a source of the antigen and a comparison to a molecular weight to enable the CD40CR antigen.

In response, Applicant submits that disclosure of sequence information for the genus of CD40CR antigens is not necessary for enablement, in view of the provision of the determinative template, CD40-Ig. The specification that enables the antigen bound by MR1 also enables the antigen bound by CD40-Ig. The specification discloses and exemplifies how to make and use CD40-Ig (*see* the specification at page 22, line 23 to page 23, line 3; page 17, line 10 to page 19, line 20; and Examples at, for example, p. 26, line 15 to page 29, line 30). Using the teachings of the specification, one of skill in the art can make CD40-Ig and use it to isolate antigens, characterize the antigens, produce antibodies that recognize the antigens, and use antibodies that recognize the antigens. Applicant has provided complete working examples, using MR1 antibody to isolate and characterize the mouse CD40CR antigen, and using CD40-Ig, which binds both CD40CR antigen

on mouse T cells and an equivalent antigen on human T cells, in addition to an enabling disclosure on how to further practice the invention. Any experimentation required to practice the methods of the invention would be routine, as the skill and knowledge in the art of antibody technology is highly advanced. Therefore, claims to uses of antibodies that recognize proteins bound by CD40-Ig are fully enabled in the specification as filed.

As discussed *supra*, no pending claim recites "CD40CR antigen." The pending claims, in essence, recite the use of antibodies that recognize a protein recognized by CD40-Ig. CD40-Ig is functional and enabled for recognizing an antigen present on activated mouse and human T cells (*see* the specification at page 22, line 23 to page 23, line 3; page 17, line 10 to page 19, line 20; and p. 26, line 15 to page 29, line 30). Applicant submits that the instant specification provides two working examples of CD40-Ig-bound antigens plus disclosure of how to make and use the invention as broadly as claimed, completely within the scope of enablement of the claims.

The Examiner cites the decision in Noelle that the skilled artisan lacked a reasonable likelihood of success in isolating human CD40CR antigen given the disclosure of mouse CD40CR antigen. As discussed *supra*, Applicant respectfully points out to the Examiner that the "reasonable likelihood of success" issue was raised by the Board while determining whether an interference-in-fact existed between the claims of the Noelle application and those of the Lederman patent. This finding was not related to the Board's determination of enablement of the invention. Moreover, Applicant submits that the human CD40CR antigen *was* identified: using the *human* CD40-Ig construct. Therefore, one of skill in the art would be able to isolate human CD40CR by utilizing the CD40-Ig construct to isolate CD40CR proteins from activated human T cells. Human CD40-Ig is a molecular tool sufficient to enable one of skill in the art to isolate human CD40CR from human T cells as well as murine T cells. Therefore, the application provides enabling disclosure for human CD40CR.

The Examiner also cites Skolnick et al. (Trends in Biotech. 18:34-39, 2000) in this enablement rejection, stating that assigning functional activities based on sequence homology is inaccurate and requires experimental research to confirm the function of a particular protein. Office

Action at page 6, paragraph 2, and again at page 8, paragraph 6. Applicant respectfully responds, as discussed *supra*, that functional activities in this application are not assigned based on sequence homology; rather, the application reveals that antigens with distinct cellular distribution and shared structural features—namely, antigens located on activated T-cells and with a structure that complements the CD40-Ig template—are capable of mediating T-cell induction of B cell activation. These functional activities were determined by experimental evidence. Antigens recognized by CD40-Ig are enabled, as discussed above. As further discussed above, the use of antibodies that bind proteins recognized by CD40-Ig is also taught in the specification as filed. Thus, Applicant asserts that the issues raised by Skolnick et al. bear no relation to enablement of the claims presented herein.

For all of the above reasons, it is clear that the specification adequately enables the claims. Reconsideration and withdrawal of this rejection is therefore earnestly requested.

Anticipation

The Examiner has rejected claims 83-86 and 90-94 as allegedly anticipated by Lederman et al. (U.S. Patent No. 5,993,816, "Lederman") under 35 U.S.C. §102(e). Office Action at 12.

The Examiner's rejection of claims 83-86 and 90-94 states that Lederman teaches methods of inhibiting humoral immune responses and autoimmunity by 5c8-specific antibodies. Today it is known that the 5c8 antibody binds a protein that is the equivalent of the CD40CR antigen, but there is no way to know this from the Lederman specification or claims as filed. Therefore, the general description of Lederman provides no teaching or suggestion of the claimed invention. Lederman does not teach use of an antibody that binds an antigen that has the same molecular weight as a protein precipitated by CD40-Ig, *and* is pre-cleared by precipitation with CD40-Ig. Lederman also does not teach that this antibody blocks binding of CD40-Ig to the antigen. In order for a reference to anticipate a claim, it must teach each and every aspect of the claims. The Lederman patent does not teach the methods of claims 83-86 and 90-94; therefore, the Lederman patent cannot anticipate these claims.

The Examiner states that the limitations as claimed would be inherent properties of the methods as taught in Lederman, and that the reference need only set forth the substance of the invention. This may be true, if at all, for the specific 5c8 antibody.

Applicant submits that the invention as claimed was conceived and completed prior to the earliest priority date of the Lederman patent, thus antedating the 5c8 antibody. Applicant submits herewith a Declaration under 37 C.F.R. § 1.131 by Randolph J. Noelle, the inventor in the present application. In the Declaration, Dr. Noelle avers that the first conception and reduction to practice of the invention occurred on or before the November 15, 1991 priority date of the Lederman patent. Therefore, Applicant submits that the specific 5c8 antibody does not anticipate the claimed invention under 35 U.S.C. § 102(e).

As the Lederman patent priority date for antibody 5c8 does not predate the claimed invention, and Lederman does not teach all limitations of the claimed invention, Lederman does not anticipate. Reconsideration and withdrawal of this rejection is therefore requested.

Obviousness

Claims 44, 46, 50, 52, 54, 57, 83-86, and 90-94 have been rejected as allegedly obvious under 35 U.S.C. § 103(a) over Lederman in view of Armitage, et al. (U.S. Patent No. 5,961,974, "Armitage"). Office Action at 12.

Applicant submits that the cancellation of claims 44, 46, 50, 52, 54, and 57 renders the rejection of these claims moot.

In response to the rejection of the remaining claims, Applicant reiterates that Lederman does not teach or suggest using an antibody having the characteristics of Applicant's antibody. To the extent the 5c8 antibody inherently may have these characteristics, Applicant again directs the Examiner's attention to the Declaration under 37 C.F.R. § 1.131 by Randolph J. Noelle. In the Declaration, Dr. Noelle states that the conception and reduction to practice of the claimed invention occurred prior to the effective date of the Lederman patent. Applicant submits that, as the

Lederman patent priority date does not predate the claimed invention, Lederman therefore cannot be part of an obviousness rejection of the claims of the instant application. And further, as the Examiner does not proffer Armitage as an anticipatory reference, Armitage alone cannot be used to reject the claims of this application.

Applicant also submits that, even if Lederman was not antedated by the Declaration herein submitted, the combination of Lederman and Armitage is improper because (i) there is no objective motivation to combine these references, and (ii) even if combined, the references do not teach every limitation of the pending claims, so these references do not make obvious the methods of the claimed invention. Lederman combined with Armitage does not teach or suggest use of an antibody that binds an antigen that has the same molecular weight as a protein precipitated by CD40-Ig, *and* is pre-cleared by precipitation with CD40-Ig. These references further do not teach or suggest that this antibody blocks binding of CD40-Ig to the antigen. In order for a combination of references to make a claim obvious, the references in combination must teach or suggest each and every aspect of the claims, with a reasonable expectation of success. Applicant submits that Lederman in combination with Armitage does not teach or suggest the methods of claims 83-86 and 90-94; therefore, Lederman in view of Armitage fails to make obvious the claims of this application.

But this places the cart before the horse. There would have been no objective basis to combine Armitage and Lederman. The Lederman application *as filed* does not mention CD40 or CD40CR; the knowledge that the disclosure of the Lederman application was directed toward these molecules was discovered subsequent to its filing, and more importantly, subsequent to Applicant's effective filing date.[7] There is similarly nothing in the Armitage patent to suggest its combination

[7]With respect to Lederman, Applicants further submit that this reference is prior art with respect to the teaching that 5c8 antigen is the same as gp39/CD40L as of its issue date, or at the earliest as of the issue date of US Patent No. 5,474,771. Relation of the 5c8 antibody to CD40L was added to the specification by an amendment (copy attached at **Tab 1**). There is no suggestion, much less an explicit teaching, in Lederman *as filed* of antibodies to gp39/CD40L, except for the specific antibody, 5c8, disclosed therein. Consequently, there can be no basis for concluding that Lederman teaches any limitation relating to CD40-Ig binding.

with Lederman, because Armitage does not provide any more than a suggestion of an antibody, much less functional characteristics of such a hypothetical antibody that would suggest any correspondence to Lederman's "antigen-unknown" 5c8 antibody. Thus, nothing in either reference would have motivated one of skill in the art at the time of filing to combine one with the other.

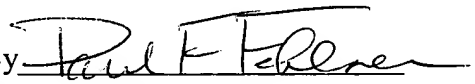
Reconsideration and withdrawal of this rejection is therefore requested.

Conclusion

Applicant respectfully requests entry of the foregoing amendments and remarks in the file history of this application. As the pending claims clearly meet the statutory requirements for patentability, this application is believed to be in immediate condition for allowance.

Dated: September 30, 2005

Respectfully submitted,

By 

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Seth Lederman, et al.

Serial No. : 07/792,728 Group Art Unit: 1805

Filed : November 15, 1991 Examiner: P. Gambel

For : MURINE MONOCLONAL ANTIBODY (5c8) RECOGNIZES A HUMAN GLYCOPROTEIN ON THE SURFACE OF T LYMPHOCYTES

30 Rockefeller Plaza
New York, New York 10112
May 23, 1994

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

AMENDMENT IN RESPONSE TO NOVEMBER 22, 1993 OFFICE ACTION AND PETITION FOR A THREE-MONTH EXTENSION OF TIME

This Amendment is submitted in response to the November 22, 1993 Office Action issued by the United States Patent and Trademark Office in connection with the above-identified application. A response to the November 22, 1993 Office Action was originally due on February 22, 1994. Applicants hereby request a three-month extension of time. The required fee for a three-month extension of time for a small entity is FOUR HUNDRED TWENTY DOLLARS ($420.00) and a check in the amount of $420.00 is enclosed. Applicants have previously established small entity status and it is still applicable. A response to the November 22, 1993 Office Action is now due May 22, 1994. However, since May 22, 1994 is a Sunday, a response filed on May 23, 1994 is timely under 37 C.F.R. §1.7. Accordingly, this Amendment is being timely filed.

Please amend the subject application as follows:

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In the Title:

Delete the title and insert the following new title:

MURINE MONOCLONAL ANTIBODY (5c8) RECOGNIZES T-B CELL ACTIVATING MOLECULE (T-BAM) (CD40 LIGAND) ON THE SURFACE OF T-LYMPHOCYTES, COMPOSITIONS CONTAINING SAME AND METHODS OF USE

In the Specification:

Page 1, line 18 Delete "refernce" and insert --reference--.

Page 1, line 19 After "known" insert --to one--.

Page 4, line 5 After "with" insert --T-B cell activating molecule (T-BAM) (now also known as CD40 ligand),--

Page 12, line 22 Delete "standrad" and insert --standard--.

Page 12, line 28 Delete "Thew" and insert --The--.

Page 32, line 32 Delete "paraformeldehyde" and insert --paraformaldehyde--.

Page 33, line 19 Delete "μCI" and insert --μCi--.

In the Claims:

Please amend claims 8-10 under the provisions of 37 C.F.R. §1.121(b) by inserting the underlined material as follows:

--8. (Amended) A monoclonal antibody of claim 1 capable of binding to the protein to which monoclonal antibody 5c8 (ATCC Accession No. HB 10916) binds.--

--9. (Amended) A monoclonal antibody of claim 1 capable of binding to the epitope to which monoclonal antibody 5c8 (ATCC Accession No. HB 10916) binds.--

--10. (Amended) The monoclonal antibody 5c8 (ATCC Accession No. HB 10916).

REMARKS

Claims 1-12, 17 and 33-34 are pending in this application.

The Title and Specification have been amended according to the suggestion of the Examiner to whom this application is assigned. The Specification has also been amended to correct obvious clerical errors. Accordingly, this amendment does not raise an issue of new matter and applicants respectfully request entry of the amendments.

Applicants acknowledge withdrawal of the rejections of claims 1-12, 17 and 33-34 under 35 U.S.C. §112, first paragraph concerning deposit of biological material and under §112, second paragraph as indefinite.

Applicants acknowledge withdrawal of the rejection of claims 1-3, 17 and 33 under 35 U.S.C. §102(b) over Rogozinski et al.

Applicants acknowledge withdrawal of the previous rejection of claims 1-4, 8-10, 17, 33 and 34 under 35 U.S.C. §102(b) or §103 over Borst et al.

Applicants acknowledge withdrawal of the rejection of claims 1-7, 11, 12, 17 and 33 under 35 U.S.C. §103 over Weiss et al. in view of Dillman.

Applicants acknowledge withdrawal of the rejection of claims 1-12, 17, 33 and 34 under 35 U.S.C. §103 over the combination of Crow et al., and Hodgkin et al., and Dillman et al.

Applicants acknowledge withdrawal of the rejection of claims 4-7, 11 and 12 under 35 U.S.C. §103 over Rogozinski et al. as applied to claims 1-3, 17 and 33 above and in further view of Dillman.

Applicants acknowledge withdrawal of the rejection of claims 5-7, 11 and 12 under 35 U.S.C. §103 over Borst et al. as applied to claims 1-4, 8-10, 17, 33 and 34 above and in further view of Dillman.

Amendment of Title and Summary

In response to the Examiner's invitation and to expedite the prosecution of this application, the Title and the Summary of the Invention have been amended to refer to the various names by which the 5c8 antigen has come to be called subsequent to applicants' invention, including "T-B cell activating molecule" (T-BAM) and "CD40 ligand" (CD40-L).

Applicants wish to emphasize that 5c8 antigen (described herein as T-BAM) was identified as a cell surface molecule that induces B cell differentiation to Ig secretion. Applicants discovered T-BAM on the basis of its essential role in contact-dependent T helper function and appreciated that pharmacologic intervention utilizing mAbs against this molecule had potential in the treatment of autoimmune diseases and allergic disorders. The murine form of T-

BAM was originally identified and termed CD40-L based on a cDNA clone of a murine protein that bound recombinant chimeric human CD40-Fc fusion protein. At that time, it was not known whether "CD40-L" was a cell surface molecule or a cytokine (secreted molecule). After applicants sequenced T-BAM protein and cloned cDNAs encoding T-BAM, the identity of T-BAM and CD40-L was clearly demonstrated. The rationale for therapeutics based on anti-T-BAM mAbs (such as 5c8) depends critically on the effects that such mAbs may have on antigen specific immune responses including autoimmune and allergic immune responses. This rationale was based on the fact that T-BAM is a cell surface molecule and not on its potential cytokine characteristics. Applicants also wish to point out that the name "CD40 ligand" may be somewhat misleading. For example, T-BAM may interact with molecules besides CD40, and CD40 may have other ligands besides T-BAM. Therefore T-BAM may be a better term because it reflects the unique role of T-BAM in immune physiology and autoimmune and allergic phenomena.

Claimed Invention Possesses Utility

The Examiner rejected claims 1-12, 17, 33 and 34 under 35 U.S.C. §101 on the grounds that the claimed anti-T-BAM antibodies and hybridomas allegedly lack utility as therapeutic agents for inhibiting the immune response or diseases or as diagnostic agents for imaging or detecting T cell tumors in vivo. The Examiner stated that when utility is directed to pharmaceutical compositions which "reads on human therapy," the data must generally be clinical, however, animal data would be acceptable in those instances where one of ordinary skill in the art would accept the correlation to human utility and there exists an art-recognized model for testing purposes. (emphasis added). With regard to human therapy, the Examiner cited Harris et al. as stating that there is widespread acceptance that there is little future for the

use of rodent monoclonal antibodies for in vivo human therapy and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses. The Examiner further stated that humanized antibodies present serious problems with immunogenicity, since the idiotype of such antibodies will contain unique amino acid sequences.

The Examiner objected to the Specification and rejected claims 1-12, 17, 33 and 34 on the grounds that the Specification allegedly fails to provide an enabling disclosure and to set forth the best mode as required under 35 U.S.C. §112, first paragraph. The Examiner indicated that the alleged insufficiency of the written description is based on inoperability of the claimed antibody for therapeutic and diagnostic use as set forth in connection with the rejection under Section 101.

In response, applicants respectfully traverse the rejections of claims 1-12, 17, 33 and 34 under 35 U.S.C. §§101 and 112, first paragraph.

Therapeutic Utility of Murine Antibody

Applicants have already presented in vitro data showing that anti-T-BAM mAb inhibits B cell activation by both Jurkat D1.1 cells (Specification, Example 3 at page 41, line 1 to page 42, line 22) and normal T cells (Specification, Example 7 at page 45, line 19 to page 47, line 20). MR1 is a hamster anti-T-BAM antibody in mouse that is similar to mAb 5c8 with respect to its ability to inhibit contact dependent activation of B cells in vitro. See **Exhibit B:** Noelle, et al., Proc. Nat'l Acad. Sci. - USA (1992) 89: 6550-6554. It is therefore anticipated that both 5c8 and MR1 would have similar biological activities in humans and mice, respectively.

Mouse anti-human T-BAM mAb 5c8 does not bind to mouse T-BAM, and conversely, hamster anti-mouse T-BAM mAb MR1 does not bind to human T-BAM. Therefore, MR1 therapy in mice is analogous to 5c8 therapy in humans. Applicants submit that testing mAb MR1 in a murine model would be accepted in the art as predictive of the effects of mAb 5c8 in humans. As evidence of the acceptance of the murine model, Durie, et al. recognized that the ability of hamster anti-murine-T-BAM mAb MR1 to inhibit inflammation in mice suggests that the "blockade of gp39 [T-BAM] function has potential therapeutic benefits for affecting the onset of autoimmune disease." **Exhibit D:** page 1330. Applicants wish to point out that there are no art-recognized primate autoimmune models, partly for ethical reasons. Because the testing cannot be done in a primate model of autoimmunity, an antibody raised against a non-primate T-BAM, such as MR1 which recognizes mouse T-BAM, is the best available animal model and would be accepted in the art.

Recently, the in vitro data presented by applicants that anti-human-T-BAM inhibits the ability of T cells to direct B cell differentiation has been confirmed in an in vivo animal model. The experiments involved the hamster monoclonal antibody MR1, which was raised against murine T-BAM (gp39). **Exhibit A:** Alfons, et al., J. Exp. Med. (1993) 178: 1555-1565 at 1562, paragraph beginning "Recently". See also, **Exhibit B:** Noelle, et al., Proc. Nat'l Acad. Sci. - USA (1992) 89: 6550-6554; **Exhibit C:** Hollenbaugh, et al., EMBO J. (1992) 11: 4313-4321. In a murine model of human autoimmune disease, anti-murine-T-BAM mAb MR1 was shown to inhibit collagen-induced arthritis. Initially, arthritis was induced in mice by intradermal injection of collagen type II. Then, three groups of eight mice received either no mAb, MR1, or irrelevant hamster Ig (HIg). "A high percentage of the untreated and HIg-treated [control] mice showed extensive distal joint inflammation; none of the anti-gp39-treated mice exhibited any signs of such

inflammation." **Exhibit D:** Durie, et al., "Prevention of collagen-induced arthritis with an antibody to gp39, the ligand for CD40," Science (1993) 261: 1328-1330. The absence of an inflammatory immune response in mice treated with anti-T-BAM antibody demonstrates that anti-T-BAM mMAb, by binding T-BAM and inhibiting its effector functions, effectively inhibited the immune response of mice receiving anti-T-BAM mAb.

The in vivo results demonstrating the therapeutic utility of an analogous anti-T-BAM monoclonal antibody (MR1) supplement the in vitro data that mAb 5c8 inhibits the ability of normal T cells to direct B cell differentiation. See Specification, page 46, line 23 to page 47, line 20; and page 51, lines 26-28. Accordingly, a person of skill in the art would accept the utility of the claimed T-BAM specific monoclonal antibody for therapeutic use.

Based on the biological activity of anti-T-BAM antibodies that prevent T-BAM binding to CD40, it was anticipated that humans with defective T-BAM molecules (i.e., that do not bind CD40) would have defective antibody production. This expectation was confirmed by the results of recent studies involving patients with X-linked immunodeficiency with normal or elevated IgM (HIGMX-1). HIGMX-1 patients have undetectable serum levels of IgG, IgA and IgE. It has been found that the presence of abnormalities in the gene for T-BAM is associated with HIGMX-1. These results demonstrate that the interaction between the B cell antigen CD40 and T-BAM expressed on activated T cells is critical for T cell driven isotype switching and the appropriate generation of antibody responses. B cells in HIGMX-1 patients are blocked at the IgM stage of differentiation because switching from IgM/IgD to other Ig isotypes is inhibited in HIGMX-1 patients, who lack a functional T-BAM. See, **Exhibit E:** Ramesh, et al., Int'l Immunol. (1993) 5: 769-773. These results constitute in vivo evidence that the lack of normal

interaction between T-BAM and CD40 inhibits B cell activation in humans, and provide further support for inhibiting an autoimmune response, such as an inflammatory response or an allergic response, in humans by inhibiting the B cell activating function of T-BAM. The antibody of this invention transiently creates a state which mimics the absence of appropriate antibody production found in HIGMX-1 patients.

Human Therapy using Murine Antibody

It is accepted in the art that murine mAbs against T cell surface molecules do possess utility in human therapy. One such antibody, OKT3, a murine mAb which binds to a T cell surface molecule, has been demonstrated to be effective in the treatment of transplanted allograft rejection and has been approved by the Food and Drug Administration (FDA). See, **Exhibit F:** Physicians' Desk Reference, pages 1594-1596. Accordingly, a person of skill in the art would believe that other monoclonal antibodies against other T cell surface molecules with unique functions (such as T-BAM) are therapeutically useful, and thus provides evidence for acceptance by those skilled in the art of the utility of mAb 5c8, or other monoclonal antibodies against T-BAM, for human therapy.

In addition to the proven utility of a murine antibody anti-T cell surface molecule antibody (OKT3) in human therapy, a person of skill in the art would appreciate that there are several features of applicants' invention which lessen the importance of the concerns identified by Harris. The Harris publication states that there is little future for the use of rodent mAbs for in vivo human therapy for three reasons: (1) the human immune response against murine proteins (HAMA response); (2) very short half-life; and (3) poor recognition of rodent immunoglobulin constant regions by human effector functions. Harris also states that repeated dosing with

chimeric antibodies is ineffective because of a residual HAMA response.

With respect to the first characteristic identified by Harris, the HAMA response, inhibition of B cell activation by mAb 5c8 renders the HAMA response less limiting to the usefulness of the claimed antibody than of murine mAbs which are not specific for a protein which regulates B cell activation, such as T-BAM which plays a unique and essential role in B cell activation. Murine mAb 5c8, which binds to human T-BAM, inhibits T helper cell activation of B cells, thereby inhibiting the animal's immune response. See Specification, page 18, line 30 to page 20, line 14; and Example 7 at page 45, line 19 to page 47, line 20. By inhibiting the immune response, anti-T-BAM antibodies inhibit the production of antibodies against themselves, as has been demonstrated for the hamster anti-mouse T-BAM mAb MR1 in mice.

This feature of the claimed invention, inhibition of the anti-antibody response, has been confirmed in an animal model that is predictive of the effects of anti-human-T-BAM in humans. Three groups of eight mice received either no antibody, hamster anti-murine-T-BAM mAb MR1, or control hamster antibody (HIg). Whereas HIg elicited a strong immune response, no anti-hamster antibodies were detected in mice treated with MR1. **Exhibit D**: Durie, et al., at 1329 middle column. In another experiment, two groups of three mice received 250 μg hamster anti-murine-T-BAM mAb MR1 (anti-gp39) or 250 μg control hamster antibody (HIg). The anti-hamster antibody response was inhibited greater than 90% in mice treated with MR1 as compared to HIg-treated mice. **Exhibit G**: Foy, et al., J. Exp. Med. (1993) 178: 1567-1575 at 1571. Thus, no anti-anti-T-BAM antibodies were detected. Accordingly, one skilled in the art would understand that mAb 5c8 or other anti-T-BAM antibodies can be administered in a therapeutic regimen that will elicit no

significant HAMA response.

The importance of the interaction between T-BAM expressed on T cells and CD40 on the surface of B cells for an adequate immune response is further confirmed by the results of studies involving patients with X-linked immunodeficiency with normal or elevated IgM (HIGMX-1), as discussed above in connection with general therapeutic utility of the antibody of this invention.

Moreover, it is known in the art to block the HAMA response by coadministering cyclosporin A together with the murine monoclonal antibody. **Exhibit H:** Weiden, et al., Cancer (Supp.) (1994) 73: 1093-1097. Accordingly, even in the event that HAMA responses were induced by mAb 5c8 or by other anti-T-BAM mAbs, this response could be inhibited by one skilled in the art by coadministration of the anti-T-BAM mAb with cyclosporin A.

Even if there would be a HAMA response, the claimed antibody would still be useful in treatment of humans with acute disease. In such cases, an anti-antibody response is not an issue because the antibody will be used in only a single treatment regimen which may include multiple administrations over the course of up to approximately 3 weeks.

With respect to the second characteristic of murine antibodies in humans identified by Harris, short half-life, the half life of anti-T-BAM antibody 5c8 is not so short as to be without therapeutic utility. Furthermore, based on the behavior of MR1 in the murine antibody response to a model peptide antigen, only a small total number of administrations may be required. MR1 had long lasting effects from only a single treatment regimen of three injections in the murine model. Intact serum MR1 could be detected for at least seventeen days after the last administration (twenty-

one days after the initiation of antibody treatment. **Exhibit G:** Foy, et al., figure 1; page 1570, sentence bridging columns, and page 1572, paragraph bridging columns. In a murine model of human autoimmune disease, hamster anti-murine-T-BAM antibody MR1 administered every 4 days prevented all signs of inflammation. **Exhibit D:** Durie, et al. at 1328, right column. See also, **Exhibit G:** Foy, et al. For purposes of illustration, even if the half-life of murine mAb 5c8 in humans is only one day, the frequency of dosing required would constitute an acceptable treatment regimen.

In addition, an ordinary artisan would take the short half-life into consideration and use or modify the antibody appropriately. For example, in one use of the claimed antibody, imaging T cell tumors (Specification, page 20, line 16 to page 21, line 19), short half-life is desirable. Moreover, physicians prescribe drugs with a short or long half-life depending on the treatment objective. In cases where a long half-life is desired, it is known in the art to extend the half-life of antibodies by coupling the antibody to agents with a longer half-life, such as polyethylene glycol (PEG). However, where a short-half life is therapeutically indicated, the physician can prescribe the uncoupled murine antibody.

The third characteristic identified by Harris, poor recognition of rodent immunoglobulin constant regions by human effector functions, does not negate the utility of this invention. The claimed monoclonal antibody binds to T-BAM, thereby inhibiting T cell effector functions. The activity of mAb 5c8, and other anti-T-BAM antibodies, depends on its binding to T-BAM and blocking the interaction of T-BAM with CD40 and not on interactions with human effector functions. Accordingly, while more efficient recognition by human effector functions enhances the efficacy of humanized T-BAM-specific antibody, T cell effector functions are inhibited even without recognition of mAb 5c8's constant region by human effector

functions.

In summary, despite Harris' statements concerning murine monoclonal antibodies generally, applicants submit that a person of skill in the art would understand that a murine monoclonal antibody which binds to a T cell surface protein necessary for B cell differentiation, such as T-BAM, is useful.

Utility of Chimeric Antibodies

In response to the Examiner's position that the chimeric antibody of claim 5 lacks utility because repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic response, please note that the murine experiments found that mice treated with anti- murine T-BAM mAb MR1 did not manifest a humoral immune response to either the idiotype or the Fc region of the hamster MR1 antibody. **Exhibit G:** Foy, et al., figure 3 and paragraph bridging columns; **Exhibit D:** Durie, et al., at 1328 middle column. Thus, anti-murine T-BAM antibody did not elicit an anti-idiotypic response. Accordingly, an anti-idiotypic response against anti-human T-BAM antibodies will not be a serious problem in humans under appropriate dosing conditions.

Applicants further wish to point out that chimeric anti-T-BAM has improved usefulness in human therapy as compared to murine anti-T-BAM because of several desirable characteristics of chimeric antibodies. First, chimeric anti-T-BAM antibody would have been expected to have the advantage of a longer half-life than its murine counterpart. Second, chimeric anti-T-BAM antibody is recognized by and interacts with human effector functions, and therefore elicits a different anti-T-BAM response. For example, a chimeric antibody with an FcγI constant region will bind complement in serum, leading to the death ("deletion") of the T-BAM-expressing

T cells. Alternatively, a chimeric antibody with an FcγIV region interacts with certain Fc receptors on different effector cells. Chimeric antibodies and techniques for making them were within the ability of the ordinary skilled artisan. See Specification, page 11, lines 13-15.

Utility of Humanized Antibodies

In response to the Examiner's position that even humanized antibodies present serious problems with immunogenicity since the idiotype of such antibodies will contain unique amino acid sequences, please note that the murine experiments found that mice treated with anti- murine T-BAM mAb MR1 did not manifest a humoral immune response to either the idiotype or the Fc region of the hamster MR1 antibody. See **Exhibit D**: Durie, et al., at 1328 middle column. Thus, anti-murine T-BAM antibody did not elicit an anti-idiotypic response, which is the only potential anti-antibody response which could limit the usefulness of humanized antibody. Accordingly, an anti-idiotypic response against anti-human T-BAM antibodies will not be a serious problem in humans under appropriate dosing conditions.

The utility of humanized anti-T-BAM antibodies is supported by the success of others in treatment using humanized monoclonal antibodies. For example, monkeys treated with a humanized anti-Tac antibody evoked anti-antibody titers that were five to ten-fold lower than the murine anti-Tac antibody and these antibodies developed later than in the murine antibody-treated monkeys. None of four monkeys developed antibodies after a single treatment with humanized anti-Tac mAb. See, **Exhibit I**: Hakimi, et al., J. Immunol. (1991) 147:1352-1359. Accordingly, using appropriate dosing conditions, humanized antibodies can be used in an effective treatment regimen without a significant anti-idiotypic response.

2-77

Furthermore, the Harris publication considers humanized antibodies to be a solution to the limitations of rodent mAbs, as recognized by applicants. Specification, page 11, lines 15-17. Harris also describes approaches to making humanized Abs that are more "human", and therefore less prone to provoking a HAMA response. See, Harris at page 42, column 3 to page 43, column 2.

Diagnostic Utility

The Examiner alleged that the evidence that mAb 5c8 binds D1.1 Jurkat cells is not convincing in showing that this antibody can be used as a diagnostic reagent to identify T cell tumors and raised the question of how one would distinguish between T-BAM-specific binding of normal cells and tumor cells (November 22, 1993 Office Action, paragraph 32).

In response, T tumor cells are distinguishable from normal T helper cells by location, by the quantity of cells in lymph nodes, and by the quantity of T-BAM molecules they express.

First, with respect to the location of T-BAM expressing cells, "T cell surface protein is formed in animals free of tumors only on the surface of activated T cells ... in the germinal centers of lymph nodes. However, the protein is found on the surface of T cell tumor cells circulating in the blood of the animal." (Specification page 20, lines 29-34). Thus, T-BAM (5c8 antigen) is not expressed on the surface of normal (non-tumor) T cells in the peripheral blood. Accordingly, the presence of T-BAM expressing cells in peripheral blood is diagnostic of an abnormality such as a tumor. Thus, the Specification describes the use of the claimed antibody in detecting and imaging T cell tumors sufficiently to enable a person of ordinary skill in the art to practice these uses without undue experimentation.

Second, there are normally very few T-BAM expressing cells even in the germinal centers of lymph nodes, and normal T-BAM expressing cells express relatively few T-BAM molecules per cell. Accordingly, an elevated number of such cells, or cells that express high amounts of T-BAM is also suggestive of tumors.

Therefore, in view of the foregoing, applicants respectfully request the Examiner to reconsider and withdraw the rejections under Sections 101 and 112, first paragraph.

Claims 5 and 6 are Defined and Enabled

The Examiner rejected claims 5-6 under 35 U.S.C. §112, first and second paragraphs.

In response, applicants respectfully traverse the rejection of claims 5-6 under 35 U.S.C. §112, first and second paragraphs.

The Examiner stated that claims 5-6 are indefinite in the recitation of "chimeric monoclonal antibody" and "humanized monoclonal antibody" because the characteristics of these antibodies allegedly are not known, particularly, which regions of the antibody are chimeric or humanized.

The Examiner also alleged that the specification does not provide a sufficient enabling description of how to make and use chimeric and humanized antibodies which possess high enough affinity for diagnostic and therapeutic procedures.

In response, the chimeric monoclonal antibody of this invention (claim 5) is defined as a "murine monoclonal antibody comprising constant region fragments from a different animal." See Specification page 25, lines 21-25. The term "chimeric monoclonal

antibody" generally means a murine antigen-binding region and a human constant region. Chimeric antibodies were well known in the art and a large number of chimeric antibodies had been made and were found to maintain their antigen specificity. Accordingly, it is well defined from the disclosure which regions are chimeric. With respect to binding affinity, because the antigen binding region is contributed by the variable region of the immunoglobulin molecule, there is no expected change in specificity or affinity by making a chimeric antibody.

The humanized mAb of this invention (claim 6) is defined as a "murine monoclonal antibody in which human protein sequences have been substituted for all the murine protein sequences except for the murine complement determining (CDR) of both the light and heavy chains." See Specification, page 11, lines 25-31. Therefore, humanized 5c8 Ab is all human amino acid residues except for the CDRs, which are derived from 5c8 and provide the binding specificity for T-BAM. Accordingly, it is well-defined from the disclosure which regions are humanized.

Furthermore, applicants submit that it would be within the ordinary skill in the art to generate other chimeric and humanized monoclonal antibodies which bind T-BAM. The mAb 5c8 secreting hybridoma is a source of mRNA encoding mAb 5c8. The sequence of the two antibody chains (heavy and light) can then be determined from isolated cDNA which encodes mAb 5c8. Using these cDNA sequences as a starting point, variant antibodies could be made using standard techniques and antibodies with sufficiently high binding affinities could be identified by comparison with mAb 5c8.

Accordingly, one possessing ordinary skill in the art would be enabled by the Specification to generate, without undue experimentation, other antibodies based on the mAb 5c8 sequence,

including chimeric and humanized antibodies, which also specifically bind T-BAM.

Therefore, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 5 and 6 under 35 U.S.C. §112, first and second paragraphs.

Applicants are the Inventors of Claimed Invention

The Examiner rejected claims 1-4, 8-10, 17, 33 and 34 under 35 U.S.C. §102(f) on the grounds that applicants allegedly did not invent the claimed subject matter. The rejection is based on Lederman, et al., "Identification of a novel surface protein on activated CD4+ T cells that induces contact-dependent B cell differentiation," J. Exp. Med. (April 1992) 175: 1091-1101. The Examiner stated that there is ambiguity as to inventorship because the above-cited publication lists as authors, in addition to the applicants, three individuals who are not named as inventors in the subject application: Alexander Krichevsky, John Belko and Julie J. Lee. The Examiner acknowledged that this publication "says nothing about inventorship." The Examiner stated that applicants must provide a satisfactory showing which would lead to a reasonable conclusion that applicants alone are the inventors of the claimed invention.

In response, applicants respectfully traverse the rejection of the claims under 35 U.S.C. §102(f). The invention claimed in the subject application was conceived solely by applicants and was reduced to practice, either by applicants directly or through persons acting under applicants' direction or supervision.

Alexander Krichevsky provided the SP2/0 fusion partner cell line and assisted applicants with the spleen fusion, an established

laboratory technique.

Both John Belko and Julie Lee worked as laboratory technicians under applicants' direction and supervision.

In view of the foregoing, applicants submit that the rejection under Section 102(f) has been overcome.

Conclusion

In summary, for the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds for objection and rejection set forth in the November 22, 1993 Office Action and earnestly solicit allowance of the claims now pending in the subject application, namely claims 1-12, 17 and 33-34.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone at the number provided.

No fee, other than the $420.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required,

authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this paper is being deposited this date with the U.S. Postal Service as first class mail addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Albert Wai Kit Chan 5/22/94

Albert Wai-Kit Chan Date
Reg. No. 36,479

Summary of the Invention

This invention provides a monoclonal antibody which specifically recognizes and forms a complex with a protein located on the surface of activated T cells and thereby inhibits T cell activation of B cells. This invention also provides the monoclonal antibody 5c8 (ATCC Accession No. HB10916).

This invention provides a human CD4- T cell leukemia cell line designated D1.1 (ATCC Accession No. CRL 10915) capable of constitutively providing contact-dependent helper function to B cells. This invention also provides an isolated protein from the surface of activated T cells, wherein the protein is necessary for T cell activation of B cells. This invention further provides an isolated, soluble protein from the surface of activated T cells, wherein the protein is necessary for T cell activation of B cells.

Monoclonal antibody 5c8 and a human CD4- T cell line, designated, D1.1 have been deposited on November 14, 1991 with the American Type Culture Collection, 12301 Parklawn Drive, Rockville Maryland, 20852, U.S.A, pursuant to the provisions of the Budapest Treaty on the International Recognition of the Microorganism Deposit for the Purposes of Patent Procedure and have been accorded ~~ATCC Accession Nos.~~ ATCC Accession Nos. HB10916 and CRL 10915 respectively.